CENTENE PHARMACY AND THERAPEUTICS
DRUG REVIEW
3Q17 July-August

BRAND NAME
Noctiva™

GENERIC NAME
Desmopressin acetate nasal spray

MANUFACTURER
Serenity Pharmaceuticals

DATE OF APPROVAL
March 3, 2017

PRODUCT LAUNCH DATE
TBD

REVIEW TYPE
☐ Review type 1 (RT1): New Drug Review
Full review of new chemical or biologic agents

☒ Review type 2 (RT2): New Indication Review
Abbreviated review of new dosage forms of existing agents that are approved for a new indication or use

☐ Review type 3 (RT3): Expedited CMS Protected Class Drug Review
Expedited abbreviated review of Centers for Medicare & Medicaid Services protected class drugs (anticonvulsants, antidepressants, antineoplastic, antipsychotics, antiretrovirals, and immunosuppressants)

☐ Review type 5 (RT5): Abbreviated Reviews for Intravenous Chemotherapy Agents
Abbreviated review for intravenous chemotherapy agents which are usually covered under the medical benefit

FDA APPROVED INDICATION(S)
Current Indication(s):
Other desmopressin formulations are approved for the following:

- DDAVP tablet – Primary nocturnal enuresis
- DDAVP Nasal Spray, Rhinal Tube, Injection, Tablet - Central cranial diabetes insipidus as antidiuretic replacement therapy
- DDAVP Injection, Stimate Nasal Spray – Hemophilia A, von Willebrand's Disease (Type I)

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New Indication(s):
For the treatment of nocturia due to nocturnal polyuria in adults who awaken at least 2 times per night to void.

OFF-LABEL USES
Not applicable

CLINICAL EFFICACY
- Nocturnal polyuria is one of several causes of nocturia. The American Urology association (AUA) defines nocturnal polyuria as the production of greater than 20% (younger individuals) to 33% (elderly individuals) of total 24 hour urine output during the period of sleep. In nocturnal polyuria, nocturnal voids are frequently normal or large volume as opposed to the small volume voids commonly observed in nocturia associated with OAB. In addition to behavioral therapy (e.g., preemptive voiding, dietary and fluid restrictions, etc.), desmopressin therapy should be considered in all cases of nocturnal polyuria.[1,2]
- The efficacy of Noctiva in patients with nocturia due to nocturnal polyuria was established in two 12-week randomized, double-blind, placebo-controlled, multi-center trials in adults at least 50 years of age. The original trials included a generalized population of patients with nocturia, but the final FDA approval in the specific population with nocturnal polyuria was based on a post-hoc subgroup analysis (approximately 80% of the initial study population had nocturnal polyuria).[3,4]
- In both trials, nocturnal polyuria was defined as a night-time urine production exceeding one-third of the 24-hour urine production confirmed with a 24-hour urine frequency/volume chart. Patients were required to have a history of at least two nocturia episodes per night for at least six months, and at least 13 documented nocturia episodes over 6 nights during screening. Notable study exclusions were those with severe daytime lower urinary tract symptoms secondary to benign prostatic hyperplasia, overactive bladder or severe stress urinary incontinence, symptomatic congestive heart failure, neurogenic detrusor overactivity, and obstructive sleep apnea.
- In Trial 1, a total of 612 patients were randomized to receive either Noctiva 1.66 mcg (n=199), Noctiva 0.83 mcg (n=209) or placebo (n=204). In Trial 2, a total of 433 patients were randomized to receive Noctiva 1.66 mcg (n=143), 0.83 mcg (n=145) or placebo (n=145). Each trial had two co-primary efficacy endpoints: (1) The change in mean number of nocturic episodes per night from baseline during the 12-week treatment period, and (2) The percentage of patients who achieved at least a 50% reduction from baseline in the mean number of nocturia episodes per night during the 12-week treatment period. The results for the co-primary efficacy endpoints among patients with nocturia due to nocturnal polyuria are shown in the table below:3

	Trial 1			Trial 2		
	NOCTIVA 1.66 mcg (N=199)	NOCTIVA 0.83 mcg (N=209)	Placebo (N=204)	NOCTIVA 1.66 mcg (N=143)	NOCTIVA 0.83 mcg (N=145)	Placebo (N=145)
Change in Mean Number of Nocturic Episodes Per Night from Baseline						
Baseline (mean)	3.4	3.4	3.2	3.3	3.4	3.4
Change from baseline †	-1.5	-1.5	-1.2	-1.5	-1.4	-1.1
Difference from placebo †	-0.3	-0.3	-	-0.4	-0.3	-
95% CI †	-0.5 to -0.1	-0.4 to 0.0	-	-0.6 to -0.2	-0.5 to -0.1	-
Percentage of Patients Achieving at Least a 50% Reduction in Nocturic Episodes per Night from Baseline						
	47%	35%	27%	49%	41%	29%
Difference from placebo ‡	21%	8%	-	20%	12%	-
95% CI ‡	12% to 30%	-0.4% to 17%		9% to 31%	1% to 23%	

*Intent-to-treat population: all randomized patients who received study drug and had at least three days of post-randomization efficacy data recorded in their diary.
CI: confidence interval
†: obtained from ANCOVA model; ‡ obtained from stratified Cochran-Mantel-Haenszel (CMH) analysis.

- At baseline, patients had approximately three nocturic voids per night, on average. The 1.66 mcg arms of Trials 1 and 2 demonstrated statistically significant reductions on both co-primary endpoints (0.3 – 0.4 reduction in the mean number of nocturic episodes per night; 20 – 21% more patients achieving at least a 50% reduction in nocturic episodes per night from baseline compared to placebo). In Trial 1, the 0.83 mcg Noctiva arm did not reach statistical significance compared to placebo on either of the co-primary endpoints.3
- Secondary efficacy endpoints in both trials included the percentage of nights during the treatment period with no nocturia and the percentage of nights during the treatment period with at most one nocturia episode. Compared to placebo, the results shown in the table below show a 5% to 6% increase in the percentage of nights with no nocturia episodes and a 9% to 15% increase in percentage of nights with at most one nocturia episode in patients treated with Noctiva 1.66 mcg.3

	Trial 1			Trial 2		
	NOCTIVA 1.66 mcg (n=199)	NOCTIVA 0.83 mcg (n=209)	Placebo (n=204)	NOCTIVA 1.66 mcg (n=143)	NOCTIVA 0.83 mcg (n=145)	Placebo (n=145)
Change from Baseline in Percentage of Nights with No Nocturia Episodes						
Baseline (mean)	0%	0%	0%	0%	0%	0%
Change from baseline †	11%	7%	5%	9%	8%	4%
Difference from placebo †	6%	2%	-	5%	4%	-
95% CI †	2% to 10%	-1% to 6%	-	1% to 9%	0.4% to 8%	
Change from Baseline in Percentage of Nights with at Most One Nocturia Episode						
Baseline (mean)	1%	1%	1%	1%	2%	1%
Change from baseline †	44%	40%	34%	45%	40%	30%
Difference from placebo †	9%	6%	-	15%	10%	-
95% CI †	2% to 17%	-1% to 13%	-	6% to 23%	1% to 18%	

- Although the change from baseline in the mean number of nocturic episodes per night relative to placebo was numerically small (0.3-0.4) and of unclear clinical significance, the findings on the 50% responder co-primary endpoint together with the secondary endpoints provide evidence of clinically meaningful benefit.4

CONTRAINDICATIONS
- Hyponatremia or a history of hyponatremia
- Polydipsia
- Primary nocturnal enuresis
- Concomitant use with loop diuretics or systemic or inhaled glucocorticoids
- Estimated glomerular filtration rate below 50 mL/min/1.73 m^2
- Syndrome of inappropriate antidiuretic hormone secretion (SIADH)
- During illnesses that can cause fluid or electrolyte imbalance
- New York Heart Association (NYHA) Class II-IV congestive heart failure
- Uncontrolled hypertension

BLACK BOX WARNINGS
Hyponatremia which may be life-threatening. Ensure serum sodium is normal before starting or resuming Noctiva. Measure serum sodium within seven days and approximately one month after initiating therapy or increasing the dose, and periodically during treatment. More frequently monitor serum sodium in patients 65 years of age and older and in patients at increased risk of hyponatremia. If hyponatremia occurs, Noctiva may need to be temporarily or permanently discontinued.

DRUG INTERACTIONS
Drugs that may cause water retention and increase the risk for hyponatremia (e.g., tricyclic antidepressants, selective serotonin re-uptake inhibitors, chlorpromazine, opiate analgesics, nonsteroidal anti-inflammatories, lamotrigine and carbamazepine)

ADVERSE REACTIONS
Common adverse reactions in clinical trials (incidence >2%) included nasal discomfort, nasopharyngitis, nasal congestion, sneezing, hypertension/blood pressure increased, back pain, epistaxis, bronchitis and dizziness.

DOSAGE AND ADMINISTRATION
The recommended dose of Noctiva in patients under 65 years old without increased risk for hyponatremia is one 1.66 mcg spray in either nostril 30 minutes before bedtime. For patients 65 and older or younger patients at risk for hyponatremia, use 0.83 mcg nightly. If needed, dose may be titrated to 1.66 mcg after at least 7 days with normal serum sodium.3

PRODUCT AVAILABILITY
3.5 mL bottle (30 effective 0.1 mL doses of either 0.83 mcg or 1.66 mcg)

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THERAPEUTIC ALTERNATIVES
None

Utilization Management Recommendation
There is significant potential for inappropriate use and utilization management should be considered for the following reason(s): i. To prevent inappropriate use of medications that have a significant potential for use that may lead to inferior or unpredictable outcomes. (1) Noctiva is the only desmopressin formulation approved for use in nocturia due to nocturnal polyuria. Use in general nocturia is not supported as the clinical trial excluded patients with conditions that may cause or contribute to nocturia (e.g., severe daytime lower urinary tract symptoms secondary to benign prostatic hyperplasia, overactive bladder or severe stress urinary incontinence, symptomatic congestive heart failure, neurogenic detrusor overactivity, and obstructive sleep apnea) (2) Noctiva is contraindicated in patients with primary nocturnal enuresis, however desmopressin tablets are FDA approved for use in this population. ii. Recommended utilization management tool(s): (check all that apply) (1) ☒ Prior authorization (2) ☐ Quantity limits (3) ☐ Provider newsletter (4) ☐ Hard block (plan exclusion) (5) ☐ Messaging (6) ☐ Electronic step therapy (7) ☐ Clinical Program
Product Comparison
• It would not be clinically appropriate to require a trial of any other desmopressin formulation prior to Noctiva. • It would not be clinically appropriate to require a trial of Noctiva prior to any other desmopressin formulation as the strengths of these products differ.

REFERENCES

[1] Cornu JN, Abrams P, Chapple CR, et al. A Contemporary Assessment of Nocturia: Definition, Epidemiology, Pathophysiology, and Management – a Systematic Review and Meta-Analysis. European Association of Urology 2012: 62; 877-890.
[2] Clinical guidelines for nocturia. The Committee for Establishement of Clinical Guidelines for Nocturia of the Neurogenic Bladder Society. International Journal of Urology (2010) 17, 397-409.
[3] Noctiva [Prescribing Information] Lakewood, NJ: Serenity Pharmaceuticals. March 2017.
[4] FDA Summary Review for Regulatory Action. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/summary_review/2017/201656Orig1s000SumR.pdf. Accessed March 20, 2017.